ORIGINAL RESEARCH PAPER

Volume-7 | Issue-5 | May-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS – A BRIEF CLINICAL GUIDE

Pharmacology

Julie B Wahlang* Assistant Professor, Department of Pharmacology, NEIGRIHMS *Corresponding Author

DK Brahma Associate Professor, Department of Pharmacology, NEIGRIHMS

Monaliza Lyngdoh Assistant Professor, Department of General Medicine, NEIGRIHMS

Arky Jane Langstieh Technical Assistant, Department of Pharmacology, NEIGRIHMS

Banylla S Nongkynrih Medical Officer, Community Health Center, Meghalaya

Parthajyoti Neog Senior Resident Doctor, Department of Pharmacology, NEIGRIHMS

ABSTRACT

There is an ever increasing need for awareness regarding the occurrence of an adverse drug reaction (ADR) and the presence of drug to drug interaction (DDI), drug-food interaction and drug-disease interaction. Drug interactions refer to an interaction which can modify the response, nullify the response or produce potentially harmful effects when two or more drugs are administered simultaneously. When two or more drugs are combined it may sometimes cause dual toxicity which may result in greater toxicity than monotherapy. Drug interactions and related adverse effects need to be considered in all clinical settings when two or more drugs are administered for a particular diagnosis. Clinicians need to be aware that early detection and recognition of ADRs occurring due to polypharmacy is important to minimize unwanted health problems. This is of paramount importance to clinicians and other health providers so that an effective treatment outcome can be reached with little or no untoward events. This in turn will be of great benefit to the population at large in reducing healthcare cost required to treat such reactions arising out of drug interactions.

KEYWORDS

Drug interactions, adverse drug reaction, drugs, clinicians, diseases

INTRODUCTION

There is an ever increasing need for awareness regarding the occurrence of an adverse drug reaction (ADR) and the presence of drug to drug interaction (DDI), drug-food interaction and drug-disease interaction. Well known definition of drug interactions refer to an interaction which can modify the response, nullify the response or produce potentially harmful effects when two or more drugs are administered simultaneously. These effects can also be seen when the reaction occurs with the presence of one drug and food or underlying medical condition of the patient.[1] Increasing new evidence has arisen regarding drug interactions among elderly patients because of polypharmacy set together with diminishing pharmacokinetics and pharmacodynamics which comes with age.[2] When two or more drugs are combined it may sometimes cause dual toxicity which may result in greater toxicity than monotherapy.[3] More thorough analytical studies that define drug interactions and the related events that occur during therapy will help with rational prescription and reduced cost of treatment which may be incurred due to unwanted drug reaction.

NATURE OF THE PROBLEM

Robertson et al (2007) have classified the reactions as 'minor' with limited consequences like in the case of Furosemide and Hydralazine. In some cases, the reactions are categorized as 'moderate' where the treatment regimen is to be administered with caution as is seen in combination regimens of antitubercular drugs. Treatment regimens are contraindicated or best avoided if the reaction is 'severe' which is based mainly on the appearance of serious and fatal toxicity like ventricular tachycardia produced by antifungal drugs combined with Cisapride. Severe blood disorders like neutropenia may be seen in pharmacodynamic interaction with antiviral combination therapy. Pharmacokinetic and pharmacodynamic interaction has been seen with combined hypolipidemic drug therapy leading to rhabdomyolysis. [4]

EXTENT OF THE PROBLEM

In a hospital based study of 44 patients over a 5-day period taking 10 to 17 drugs, 77 potential drug interactions were identified, but only one probable and four possible types of adverse reactions (6.4%) were detected.[5] A further study among patients taking anticonvulsant drugs found that 6% of the cases of toxicity were due to drug interactions. [6] An Australian study found that about 10% of hospital admissions were due to drug interactions. It is estimated that DDI contributes to about 6 - 30% of all ADRs. Furthermore, ADR due to DDI accounts for about 2.8% of hospital admission every year. In a recent review, it has been reported that approximately 0.05% of the emergency department visits, 0.6% of the hospital admissions and 0.1% of the re-hospitalizations are caused by ADRs due to DDIs.[7] The rate of DDIs in patients treated in the intensive care (54%) has been reported to be twice that of patients treated in the wards.[8] There is an overall increase risk in this setting as additional drugs being included with existing drug therapy. Carbonin et al. (1991) observed a strong exponential relation between the risks of ADRs and the number of drugs prescribed.[9]

Nikica et al. (2011) reported 1209 reports involving spontaneous reporting database of at least two drugs. There were 468 reports on potential drug-drug interactions and 94 of such reports were actual drug-drug interactions, out of which 53 of 94 such reports showed adverse drug reactions indicating that these areas need to be the focus of health care awareness among clinicians.[10] The prevalence of potential drug interactions of 3.7% has been reported among pediatric age groups and the risks increase with the important diseases like epilepsy, leukemia and rheumatoid arthritis treated with various drugs.[11]

With regards to elderly population, Piper et al. (1991) reported that patients of over 65 years of age hospitalized for peptic ulcer or upper GI bleed have been reported with the use of oral corticosteroids and NSAIDs users carry a higher RR of peptic ulcer disease compared with non users of NSAIDs (RR: 1.1).[12] Hence medical supervision of elderly patients treated with NSAIDs concomitantly with drugs for heart failure even though for short periods needs to be emphasized.

Reports which are available today rarely mention the prevalence of adverse events in relation to the drug-drug interactions. This may lead

to less estimated numbers of actual events occurring at the time of drug intake. It has been viewed that non-communicable diseases (NCDs) were seen to be in the top ten causes of mortality worldwide which is expected to rise by 76% by 2030. [13] Medications are vital to therapy for chronic diseases to alleviate pain and improve quality of life provided such treatment do not bring about hazards of adverse events.[3]

Most authors have commented that ADRs occur during hospital stay, though such studies are mostly retrospective and major evaluation may be missed at the time of occurrence which may have been prevented.[14] Harugeri et al. (2011) estimated that the total cost of hospital stay due to ADRs amount to the US $4350 (INR 200100).[15] Clinicians need to be aware that early detection and recognition of ADRs occurring due to polypharmacy is important to minimize unwanted health problems during clinical care.

PHARMACOKINETIC INTERACTIONS AND ADRS

Busca et al (2013) have reported that 78% of patients showed potential drug interaction and some commonly prescribed drugs are mentioned here. [14]

Drugs	Interactions	Adverse Reactions
Diclofenac and Ramipril	Altered renal function	Increase in Creatinine level
Acenocoumarol and Fenofibrate	Binding to CYP450-3A4 enzyme	Blood disorders
Perindopril and Ketoprofen	Renal function altered	Renal toxicity
Acenocoumarol and Simvastatin	Binding to CYP450-3A4 enzyme	Spontaneous hematoma
Digoxin and Amiodarone/Verapamil	Increased concentration of Digoxin	Digoxin toxicity
Simvastatin and Fluconazole	Inhibition of metabolism of Simvastatin	Myalgia
Amitryptyline and Tramadol	Inhibition of metabolism of Tramadol	Headache
Sotalol and Amiodarone	Additive effect	QT Prolongation
Metoprolol and Amiodarone	Inhibition of metabolism of Metoprolol	Bradycardia
Metoprolol and Amlodipine	Additive cardiovascular effects	Hypotension

PHARMACOKINETIC INTERACTIONS AND ADRS IN SPECIAL CASES

a. Cancer Chemotherapy (Josephine Sasu-Tenkoramaa and Jeffrey Fudin) [16]

It has been reported that about one third of patients treated with chemotherapy for various types of cancers suffer from drug reactions which may be attributed to combination therapy. However, very few reports have been published with definite and concrete evidences.

1. Methotrexate and NSAIDs : Decrease renal clearance of Methotrexate
2. Imatinib and Fentanyl : Increased bioavailability of Fentanyl =sedation, hypotension
3. Methotrexate and Celecoxib : Increase concentration of Methotrexate
4. Imatinib and Methadone : Increased Methadone concentration
5. Imatinib and Diclofenac : Increased levels of Imatinib
6. Cisplatin and Meloxicam : Increased level of Cisplatin
7. Doxorubicin and Methadone : Additive cardiotoxic effects
8. Nilotinib and Morphine: Increased concentration of Morphine = Morphine toxicity
9. Imatinib/Nilotinib/Dasatinib and Tramadol : Inhibits metabolism of Tramadol
10. Imatinib and Venlafaxine : Increased concentration of Venlafaxine
11. Doxorubicin/ daunorubicin/ Epirubicin and Venlafaxine/ Amitryptyline : Predispose to QTc Prolongation

b. Kidney Disease (Alessandra Batista Marquito et al) [17]

1. Metformin and Nifedipine : Increased Metformin absorption = Increased Metformin toxicity
2. Allopurinol and Captopril/ Enalapril : Hypersensitivity reactions = Stevens Johnson syndrome
3. Captopril and Furosemide : Postural hypotension
4. Nifedipine and Phenytoin : Decreased metabolism of Phenytoin = Increased Phenytoin toxicity

DRUG INTERACTIONS AND ADRS SCREENING INFORMATION

1. Screening Program Software: Lexi-Interact, Micromedex Drug Interactions, iFacts, Medscape, Drug Interaction Fact software and Epocrates
2. Stockley's Drug Interaction: The golden book which deals with different aspects of drug interactions.

There has been much debate on the sensitivity and effectiveness of the currently available screening programs. Recent report evaluated that among all the above software programs the comparative scores of accuracy and comprehensiveness were seen to be highest with Lexi-Interact and Micromedex.[18]

CONCLUSION

Drug interactions and related adverse effects need to be considered in all clinical settings when two or more drugs are administered for a particular diagnosis. Many of these interactions are preventable and can be avoided with proper knowledge of the prescriber and adequate precautionary measures thereby preventing hazards to the patient. This is of paramount importance to clinicians and other health providers so that an effective treatment outcome can be reached with little or no untoward events. This in turn will be of great benefit to the population at large in reducing healthcare cost required to treat such reactions arising out of drug interactions.

CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

References

1. Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013 Sep 30.
2. Lal H.M, Lal U. Drug Interactions - Mechanisms and Clinical Implications. In: S.K. Bichile, editor. API, Medicine Update. 18: 670-690, Chapter 89; 2008.
3. Brahma DK, Wahlang JB, Marak MD, Sangma MC. Adverse drug reactions in the elderly. Journal of pharmacology & pharmacotherapeutics. 2013 Apr;4(2):91.
4. Robertson S, Penzak SR, Huang SM. Drug interactions. In Principles of Clinical Pharmacology (Third Edition) 2013 (pp. 239-257).
5. Schuster BG, Fleckenstein L, Wilson JP, Peck CC. Low incidence of adverse reactions due to drug-drug interactions in potentially high-risk population of medical inpatients. In clinical research 1982 Jan 1 (Vol. 30, No. 2, pp. A258-A258). 6900 Grove RD, Thorofare, NJ 08086: SLACK INC.
6. Manon-Espaillat R, Burnstine TH, Remler B, Reed RC, Osorio I. Antiepileptic drug intoxication: factors and their significance. Epilepsia. 1991 Feb 1;32(1):96-100.
7. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj. 2004 Jul 1;329(7456):15-9.
8. Uijtendaal EV, Harssel LL, Hugenholtz GW, Kuck EM, Zwart-van Rijkom JE, Cremer OL, Egberts TC. Analysis of Potential Drug-Drug Interactions in Medical Intensive Care Unit Patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2014 Mar 1;34(3):213-9.
9. Carbonin P, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients. Journal of the American Geriatrics Society. 1991 Nov 1;39(11):1093-9.
10. Mirošević Skvrce N, Macolić Šarinić V, Mucalo I, Krnić D, Božina N, Tomić S. Adverse drug reactions caused by drug-drug interactions reported to Croatian Agency for Medicinal Products and Medical Devices: a retrospective observational study. Croatian medical journal. 2011 Oct 15;52(5):604-14.
11. P, Prokeš M, Konvalinka M, Fürstová J, Urbánek K. Incidence of potential drug interactions in medication prescriptions for children and adolescents in the University Hospital Olomouc, Czech Republic. European journal of pediatrics. 2013 May 1;172(5):631-8.
12. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Annals of Internal Medicine. 1991 May 1;114(9):735-40.
13. World Health Organization, editor. Global tuberculosis report 2013. World Health Organization; 2013.
14. Bucşa C, Farcaş A, Cazacu I, Leucuta D, Achimas-Cadariu A, Mogosan C, Bojita M. How many potential drug–drug interactions cause adverse drug reactions in hospitalized patients. European Journal of Internal Medicine. 2013 Jan 1;24(1):27-33.
15. Harugeri A, Parthasarathi G, Ramesh M, Guido S, Basavanagowdappa H. Frequency and nature of adverse drug reactions in elderly in-patients of two Indian medical college

hospitals. Journal of Postgraduate medicine. 2011 Jul 1;57(3):189.
16. Josephine Sasu-Tenkoramaa and Jeffrey Fudin. Drug Interactions in Cancer Patients Requiring Concomitant Chemotherapy and Analgesics. Practical Pain Management. May 2013. Vol 13,Issue : 4. Available from https://www.practicalpainmanagement.com/issue/1304
17. Marquito AB, Fernandes NM, Colugnati FA, Paula RB. Identifying potential drug interactions in chronic kidney disease patients. Jornal Brasileiro de Nefrologia. 2014 Mar;36(1):26-34.
18. Kheshti R, Aalipour M, Namazi S. A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness. Journal of research in pharmacy practice. 2016 Oct;5(4):257.